Topical Bevacizumab in the Treatment of Corneal Neovascularization

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Topical Bevacizumab in the Treatment of Corneal Neovascularization: Results of a Prospective, Open-label, Non-comparative Study

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Abstract

Objectives—To study the safety and efficacy of topical bevacizumab in the treatment of corneal neovascularization (NV).

Design—In a prospective, open-label, non-comparative study, 10 eyes from 10 patients with stable corneal NV were treated with topical bevacizumab 1.0% for 3 weeks and followed up to 24 weeks.

Main Outcome Measures—The primary safety variables were the occurrence of ocular and systemic adverse events throughout the course of the study. The primary efficacy variables were neovascular area (NA), measuring the area of the corneal vessels themselves; vessel caliber (VC), measuring the mean diameter of the corneal vessels; and invasion area (IA), measuring the fraction of the total corneal area covered by the vessels.

Results—From baseline visit to the last follow-up visit, the mean reduction was 47.1% ± 36.7% for NA, 54.1% ± 28.1 for VC, and 12.2% ± 42.0% for IA. The decreases in NA and VC were statistically significant ($p = 0.0014$ and $p = 0.00009$, respectively). However, changes in IA did not achieve statistical significance ($p = 0.19$). Visual acuity and central corneal thickness showed no significant changes. Topical bevacizumab was well-tolerated with no adverse events.

Conclusions—Short-term topical bevacizumab therapy reduces the severity of corneal NV without local or systemic side-effects.

Application to Clinical Practice—Topical bevacizumab provides an alternative therapy in the treatment of stable corneal neovascularization.

Trial Registration—clinicaltrials.gov Identifier: NCT00559936

The cornea has the unique feature (except for cartilage) of being normally avascular, but under pathologic conditions vessels invade the cornea from the limbal vascular plexus. A wide variety of insults including infection, inflammation, ischemia, degeneration, trauma, and loss of the limbal stem cell barrier can cause corneal neovascularization (NV).[1] Although corneal NV can occasionally serve a beneficial role in the clearing of infections, wound healing, and in arresting stromal melts,[2] its disadvantages are numerous. Corneal NV often leads to tissue scarring,

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edema, lipid deposition, and persistent inflammation that may significantly alter visual acuity.[3] Based on data derived from the Massachusetts Eye and Ear Infirmary in 1996, it is estimated that for any given year, 1.4 million patients in the US develop corneal NV, among whom 12% of cases are associated with a decrease in visual acuity.[4] Twenty percent of corneal specimens obtained during corneal transplantation show histopathologic evidence of NV.[5] Corneal NV accompanies the most common causes of corneal infectious blindness in both the developed (herpetic keratitis)[6] and developing (trachoma and onchocerciasis) world,[7] which cause millions to lose their sight. Corneal NV is also notable in extended-wear usage of hydrogel contact lenses.[8, 9] The prevalence of neovascularization ranges from 125,000 to 470,000 people in the US who wear soft lenses for refractive correction.[4] All these data indicate that corneal NV is a significant contributor to eye disease.

Corneal NV may not only reduce visual acuity but also it results in the loss of the immune privilege of the cornea, thereby worsening the prognosis of subsequent penetrating keratoplasty (PK).[10] Preexisting corneal stromal blood vessels have been identified as strong risk factors for immune rejection after corneal transplantation.[11, 12] For instance, whereas the success rate of corneal transplantation in low-risk avascular beds surpasses 90%, the survival rates are drastically lower in high-risk neovascularized beds in which corneal grafts suffer from rejection rates far worse than first kidney or heart allografts.[11, 12]

Current treatments for corneal NV including medications, such as steroids or non-steroidal anti-inflammatory agents, laser photocoagulation, fine-needle diathermy, photodynamic therapy, or restoration of the ocular surface with the use of conjunctival, limbal, or amniotic membrane transplantation have demonstrated variable and largely limited clinical success.[1] The highly variable efficacy and myriad side-effects (cataract, glaucoma, and increased risk of infection) of topical and systemic corticosteroids are well known to clinicians who use these agents regularly in trying to arrest these disease processes. Other treatment modalities are often ineffective, or vessel recanalization occurs requiring multiple treatment sessions which can lead to serious side effects. Furthermore, none of these treatments specifically target the molecular mediators of angiogenesis.[13]

Vascular endothelial growth factor (VEGF) is thought to be a key mediator in the process of neovascularization.[13] The prominent role of VEGF in the pathophysiology of corneal NV has been demonstrated in experimental models of corneal NV.[14] It has been shown that VEGF is up-regulated in inflamed and vascularized corneas in humans and in animal models.[15] It has also been shown that inhibition of angiogenesis by neutralization of VEGF can promote corneal graft survival in animal models.[16] VEGF inhibitors such as pegaptanib sodium (Macugen; [OSI] Eyetech/Pfizer, Inc, New York, NY), ranibizumab (Lucentis; Genentech Inc., San Francisco, CA) and bevacizumab (Avastin; Genentech Inc., San Francisco, CA) are currently used for the treatment of neovascular age-related macular degeneration (AMD).[17] The first two agents have been approved by the FDA for use in neovascular AMD; the third drug which is a full-length humanized antibody against VEGF, has been approved for use in oncology but is also widely used off-label to treat choroidal neovascularization,[18] central retinal vein occlusion,[19] proliferative diabetic retinopathy, [20] and iris neovascularization [21] with encouraging results. Bevacizumab has now been widely adopted and is arguably part of the standard of care for the treatment of neovascular AMD for many patients.[17, 18]

Recently, off-label use of topical as well as subconjunctival bevacizumab has also been considered as a new treatment modality for corneal NV.[22–27] While there is substantial evidence for the intravitreous administration of bevacizumab in the treatment of choroidal NV, data regarding the safety and efficacy of topical bevacizumab in the treatment of corneal NV are, as yet, preliminary. Topical bevacizumab was demonstrated to inhibit corneal NV after chemical injury in an experimental rat model.[24] In humans, a small number of studies showed

that topical bevacizumab can reduce corneal NV in a few patients with significant corneal NV.[25, 26] However, many aspects of topically administered bevacizumab in the treatment of corneal NV, including long-term safety and efficacy against actively growing as well as established corneal NV, optimal dosing for modulating the neovascular process, and long-term stability of treatment results, have not been well known. The purpose of this article is to report the long-term (6 months) results of safety, efficacy, and stability of treatment of clinically stable corneal NV in 10 patients using topical bevacizumab in a prospective, open-label clinical study.

MATERIALS AND METHODS

Study Design

This was an open label, single site, uncontrolled, single group assignment, safety/efficacy study of topical administered bevacizumab in subjects with corneal NV. This study was approved by the Institutional Review Board of the Massachusetts Eye and Ear Infirmary. Potential patients signed an informed consent at the time of screening visit.

Patients—Adult patients of either sex were eligible for participation if they had clinically stable corneal NV as defined below. Patients with superficial or deep corneal NV that extended farther than 2 mm from the limbus were considered. However, all of the following conditions were excluded before a corneal NV was regarded as clinically stable: (i) current or recent (≤3 months) episode of corneal and ocular surface infection (bacterial, viral, fungal, or acanthamoebal); (ii) ocular surgery in study eye, including cataract surgery, full thickness or lamellar keratoplasty, ocular surface reconstruction, limbal stem cell transplantation, or amniotic membrane transplantation within 6 months prior to study entry; (iii) current or recent (≤3 months) use of contact lens; (iv) current or recent (≤3 months) persistent corneal epithelial defects (of at least 14 days in duration measuring more than 1 mm^2). Other exclusion criteria are listed in Table 1. Qualified patients who met the above criteria were invited to participate in the study, and if consented were enrolled consecutively to begin the course of topical bevacizumab. The study eye was identified at the screening visit. If both eyes were eligible for the study, the eye worst affected by corneal NV was selected for entry into the study.

Study Medication—Topical bevacizumab solution was formulated and aseptically prepared from commercially available intravenous bevacizumab (Avastin; Genentech Inc., San Francisco, CA), and transferred into a sterile, light-protected dropper container by the Massachusetts Eye and Ear Infirmary pharmacy. Based on the earlier case-report study on the efficacy and safety of topical bevacizumab[26], a similar formulation of 1.0% (10mg/ml) concentration of bevacizumab with 0.01% (0.1mg/ml) benzalkonium chloride with a pH of 6.2 was used. The patients were instructed to refrigerate the study drugs at 2°C – 8°C (36°F – 46° F). To reduce the chance of systemic absorption of bevacizumab, both puncta of the study eye were temporarily plugged for the duration of treatment (3 weeks). The dosing of topical bevacizumab 1% used was two and four times a day. To avoid the potential systemic and local side effects of long-term VEGF blockade, the treatment course was limited to 3 weeks. During the study, all concomitant medication treatment regimens were kept as constant as permitted by accepted medical practice.

Study Protocol—Follow-up visits were scheduled at week 1, 3, 6, 12, and 24. At all visits, in addition to a comprehensive eye examination, a detailed review of medical and ophthalmic histories and current medications was recorded. Central corneal thickness was also measured by ultrasonic pachymeter at all visits. Digital corneal photographs at the slitlamp microscope were taken at the screening visit as well as visits in weeks 3, 6, 12, and 24. Systolic and diastolic blood pressure measurement was obtained at all visits. This study did not include blood sampling or any pharmacokinetic measures.

Outcomes Measures

Safety—Safety was monitored via occurrence of adverse events. All adverse events (ocular and systemic) were monitored and recorded throughout the course of the study, including seriousness, severity, action taken, and relationship to study treatment. Ocular adverse events were identified by eye examination, visual acuity testing, intraocular pressure, biomicroscopy and corneal fluorescein staining through week 24; systemic adverse events were identified by physical examination, subject reporting, and changes in vital sign (blood pressure) through week 24.

Efficacy—The primary efficacy variables were the size and extent of corneal NV. By comparing baseline corneal photographs with the follow-up photographs as detailed below, the efficacy of bevacizumab in treatment of corneal NV was evaluated. Other efficacy variables included measuring the changes in best corrected visual acuity and central corneal thickness from baseline to the last visit.

Quantification of Corneal Neovascularization—Three primary metrics for corneal NV (Fig. 1) were considered. The first, referred to as "Neovascular Area (NA)," involves measuring the area of the corneal vessels themselves when projected into the plane of a photograph. The second metric, referred to as "Vessel Caliber (VC)," involves determining an approximate mean diameter of the corneal vessels. The third metric, referred to as "Invasion Area (IA)," measures the fraction of corneal area in which vessels are present. Digital slit-lamp corneal pictures were analyzed morphometrically using graphics editing software (Photoshop® CS2; Adobe Systems Inc.) and a mathematical program (written using Matlab®; Mathworks Inc.). After the total corneal area was outlined, by applying the same graphical editing procedure, the blood vessels were enhanced and traced by using Photoshop tools and filters. By setting a threshold level, the non-vessel area was erased, and the remaining neovascular area was then pixelized and measured (Fig. 1A). Finally, the calculated blood vessel area was normalized to the whole corneal area to obtain the NA score for each corneal picture. We also estimated VC by using a computational technique to measure the largest diameter circle centered at each pixel inside a blood vessel, the mean value across all pixels within blood vessels was taken as an estimate of the mean VC for a given image. Lastly, the IA was also quantified; the very ends of all vascular sprouts were marked, and by connecting all these marks, the contour of the IA was traced and the measured area was again normalized to the whole corneal area.

Statistical Methods—In order to assess changes in the three metrics, three different time points were considered: (i) the initial (screening) visit, (ii) the 3-week visit (end of treatment), and (iii) the last follow-up visit. Paired t-tests were performed with one-sided alternatives comparing cohort scores for each metric individually. In each case, the one-sided alternative hypothesis was that there was a reduction in cohort scores for a given metric from the earlier time point to the later time point. A P value ≤ 0.05 was considered statistically significant.

RESULTS

Ten eyes of 10 patients (4 males and 6 females) with stable corneal NV were included in this study. The demographic characteristics of the study population including age, gender, eye, background disease for corneal NV, and the frequency use of topical bevacizumab are listed in Table 2. The mean (±SD) age was 46.7 (±13.7) years, ranging between 23 to 71 years. The mean (±SD) follow-up period was 22.8 (±3.8) weeks, ranging between 12 to 24 weeks.

Neovascular Area

The patient population showed a significant reduction in NA from the screening visit to the last visit ($p = 0.0014$) (Fig. 2A). The 95% confidence interval for change in NA was 25.9% to

100% reduction. The mean (±SD) reduction seen across the cohort in NA was 47.1% (±36.7%), ranging between 11% to 98%. A significant decrease was also found in NA from the screening visit to the 3-week visit (end of treatment), with p = 0.031. The mean (±SD) change in NA from the initial visit to the 3-week visit was 27.8% (±41.4%). Lack of significant change in NA from the 3-week visit to the last visit when tested against a two-sided alternative (p = 0.27) indicates stability of the treatment result.

Vessel Caliber

The subjects showed a significant reduction in VC from the screening visit to the last visit (p = 0.00009) (Fig. 2B). The 95% confidence interval for 12 change in VC was 37.8% to 100% reduction. The mean (±SD) reduction seen in VC was 54.1% (±28.1%), ranging between 22% to 99%. The reduction in VC from the initial visit to the 3-week visit was not found to be significant (P = 0.12). However, there was a significant decrease (p= 0.0076) seen in VC from the 3-week visit to the last visit indicating a slightly delayed, but sustained treatment outcome. The mean (±SD) change in VC from the 3-week visit to the last visit was 35.2% (±37.2%).

Invasion Area

The mean (±SD) change in IA was 4.4% (±52.0%) and 12.2% (±42.0%) from the baseline visit to the 3-week visit and to the last visit, respectively. No statistical significant change was seen in IA, whether from the initial visit to the 3-week visit (p = 0.30) or from the initial visit to the last visit (p = 0.19) (Fig. 2C).

Twice Daily vs. Four Times Daily Dose Regimens

No significant difference was seen in the therapeutic responses (for any of the three metrics used) between patients using bevacizumab four times a day (n= 5) compared with those using the drug twice daily (n=5) (P-values were 0.17 for NA, 0.07 for VC, and 0.09 for IA).

Other Endpoints and Adverse Events

All visual acuity data were converted to logMAR equivalents of Snellen acuity for the purpose of analysis. Mean (±SD) corrected logMAR visual acuity was 0.65 (±0.49) at the screening visit, 0.68 (±0.52) at the 3-week visit, and 0.63 (±0.60) at the last visit. Changes in visual acuity from baseline to any of the follow-up visits were not found to be significant. Mean (±SD) values for central corneal thickness were 481.9 (±90.6) microns at the baseline, 487.3 (±94.3) microns at the 3-week visit, and 499.7 (±93.2) microns at the last visit, with no statistically significant difference observed among these.

Mean arterial pressure (MAP){= [(2 × diastolic) + systolic] / 3} at 1 week, 3 weeks, and last visit were compared to the baseline visit. The mean (±SD) of MAP for all patients was 90.8 (±8.9) mmHg at the baseline, 88.6 (±6.4) mmHg at 1 week (p = 0.42), 84.4 (±6.2) mmHg at 3 weeks (p = 0.09), and 93.5 (±11.9) mmHg at the last visit (p = 0.50). No significant changes were found in MAP at any follow-up visit. No systemic or ocular adverse events, including thromboembolic events, hemorrhage, allergic reaction, ocular surface toxicity and epitheliopathy (superficial punctate keratopathy, epithelial erosion or defect,), or burning on instillation, were reported. Interestingly, self-reported compliance was extremely favorable; only 3 patients missed 1 or 2 doses of bevacizumab throughout the entire treatment period.

COMMENT

VEGF has demonstrated an intimate connection with the pathogenesis of corneal NV.[15] In animal models of corneal NV, increased expression levels of VEGF and VEGF receptors have been confirmed.[14, 28, 29] In humans, pathological studies have confirmed that VEGF and its

receptors are present in higher concentrations in corneal buttons with NV than in normal corneas, irrespective of the cause of neovascularisation.[15, 30] Furthermore, VEGF blockade, at both the protein and mRNA level, has been shown to reduce corneal NV and improve corneal graft survival in experimental animals.[16]

Bevacizumab is a full-length, recombinant humanized monoclonal immunoglobulin G1 (IgG1) that binds to and inhibits the activity of VEGF-A, thereby inhibiting angiogenesis.[31] It was the first anti-VEGF antibody to be approved by the U.S. Food and Drug Administration specifically for the treatment of metastatic colon cancer, and recently, for non-small cell lung cancer and metastatic breast cancer.[32] Off-label intravitreal administration of bevacizumab for treatment of choroidal NV[18] has gained wide and rapid acceptance because of its safety, efficacy, and lower cost in comparison to other anti-VEGF drugs.

In the aggregate, the present study shows that topical bevacizumab 1% is effective in the treatment of clinically stable corneal NV as evidenced by a nearly 50% reduction in 2 corneal NV metrics (NA and VC). In the two-dimensional plane of a corneal photograph, if vessel area (NA) is regarded as a function of mean vessel width (VC) and total vessel length, it would appear that the reduction in VC accounted for most of the improvement that was seen in NA. Furthermore, the absence of meaningful change in IA in our study indirectly supports the conclusion that significant narrowing of blood vessels rather than reduction in blood vessel length is the main outcome of anti-VEGF therapy in corneal NV. VEGF acts at several levels on vascular beds: it is a survival factor for endothelial cells, it is a potent vasodilator, and it increases microvascular permeability.[33] VEGF, once considered as vascular permeability factor (VPF),[34] was later found to promote endothelial cell growth.[35] VEGF, therefore, renders the microvasculature hyper-permeable to circulating macromolecules with a potency about 50,000 times greater than histamine.[34] Therefore, the vascular stabilization (reduction in vascular permeability) affected by anti- VEGF therapy may diminish the vascular flow rate, causing reduction in the caliber of blood vessels.

The study shows a highly variable efficacy across the cohort treated with bevacizumab (Fig. 3, Fig. 4, 5), which is evidenced by the high standard deviations of the computed corneal NV metrics. The level of therapeutic response in case 6 (almost a complete resolution of corneal NV as shown in Figure 3) and case 8 (a very modest therapeutic response to the anti-VEGF treatment as shown in Figure 5) exemplify the therapeutic spectrum of topical bevacizumab in the treatment of corneal NV. Several hypotheses may explain this variability in response to topical bevacizumab, including heterogeneity in corneal NV etiologies, variable levels of VEGF expression in the pathobiology of diverse cases, and variable levels of drug penetration.

Topical application is the preferred method of administration of a drug to the cornea and ocular surface. However, topical treatment will only be effective if the drug can penetrate through the corneal epithelial barrier to reach the target tissues within a therapeutic level. Topical administration of full-length immunoglobulins, such as bevacizumab with a molecular weight of 149kD, is typically considered ineffective because such molecules are too large to penetrate the intact corneal epithelium. However, epithelium over the neovascularized area can be defective, particularly in patients with ocular surface disease which interferes with normal corneal epithelial function and results in incompetent barrier function.[36] Our recent work in a mouse model of corneal NV has clearly demonstrated that bevacizumab can penetrate the neovascularized cornea after topical application (Sadrai, Z, et all. *Invest Ophthalmol Vis Sci* 2008;49: ARVO E-Abstract 1488). In view of the size of the bevacizumab molecule, however, the degree of inadequacy of the corneal epithelial barrier likely varies to a large extent from one vascularized cornea to another.

Our study did not show any systemic or local adverse effects. Systemic blood pressure remained stable at the baseline level, and no serious life-threatening side effects occurred during the follow-up period. This shows that topical bevacizumab 1%, in both twice daily and four times a day regimens, is safe. This finding, however, may be due in part to the precautions applied to our study, such as the placement of punctal plugs and the exclusion of any patient aged 75 or older or having a history of hypertension, diabetes mellitus, or thromboembolic event. Similarly, from an eye standpoint, topical bevacizumab 1% (with benzalkonium 0.01% as a preservative) was tolerated very well in all patients. No local irritation, allergic reaction, or surface epitheliopathy was observed. This is in contrast with a 60% rate of spontaneous loss of epithelial integrity as recently reported by Kim et al.[25] In this report, the investigators used topical bevacizumab at a slightly higher concentration (1.25%) twice daily for a much longer period (3 months), and adverse effects generally appeared during the second month of treatment.[25] This suggests that the duration of treatment may well determine the safety of topical bevacizumab.

While anti-VEGF therapy shows efficiency in treating corneal NV, VEGF has desirable effects that may be blocked by bevacizumab therapy. These include the capacity to promote the formation of collateral vessels, to control vascular tone, to affect corneal nerve regeneration,[37] and a substantial role in wound healing.[38] In this regard it is important to note that the long-term neutralization of VEGF may have unintended local or systemic consequences that our study has not yet determined. Prolonged blockade of VEGF may impair wound healing and the regeneration of corneal nerves, which may cause a loss of epithelial integrity in cornea. Although delivered in a small dose on the surface of the eye, anti-VEGF drugs could also pass into the systemic circulation. Hypertension, proteinuria and various cardiovascular events are potential consequences of the systemic inhibition of VEGF.

In summary, the significant narrowing of corneal blood vessel diameter and diminishing neovascular area in response to topical bevacizumab therapy provides evidence that anti-VEGF therapy could offer an alternative or adjunctive measure to conventional therapies in the treatment of stable corneal neovascularization. However, further research using larger patient cohorts is warranted to determine the exact dosage and indications for use.

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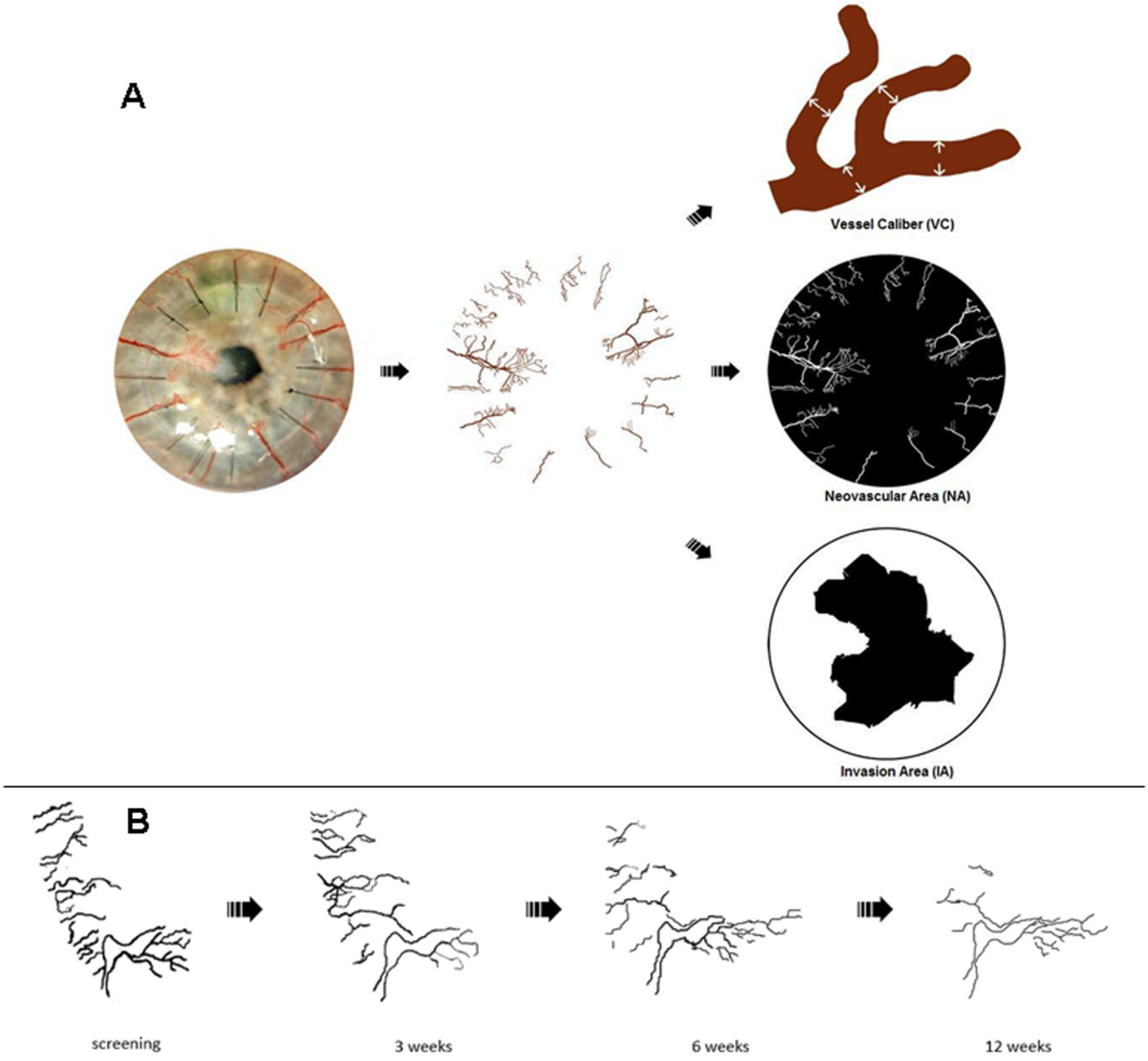

Figure 1.

Quantification of corneal neovascularization. **A**, Digital slit-lamp corneal pictures were analyzed using graphics editing software (Photoshop) and a mathematical program (Matlab script). After the total corneal area was delineated, the blood vessels were isolated using Photoshop. In order to analyze the efficacy of bevacizumab in treating corneal NV, three metrics were computed using a Matlab script: Neovascular Area (NA), which measures the area of the corneal vessels themselves; Vessel Caliber (VC), which determines an approximate mean diameter of the corneal vessels; Invasion Area (IA), which measures the fraction of corneal area in which vessels are present. **B**, Changes in corneal vessels (patient 4) at different time points after the treatment.

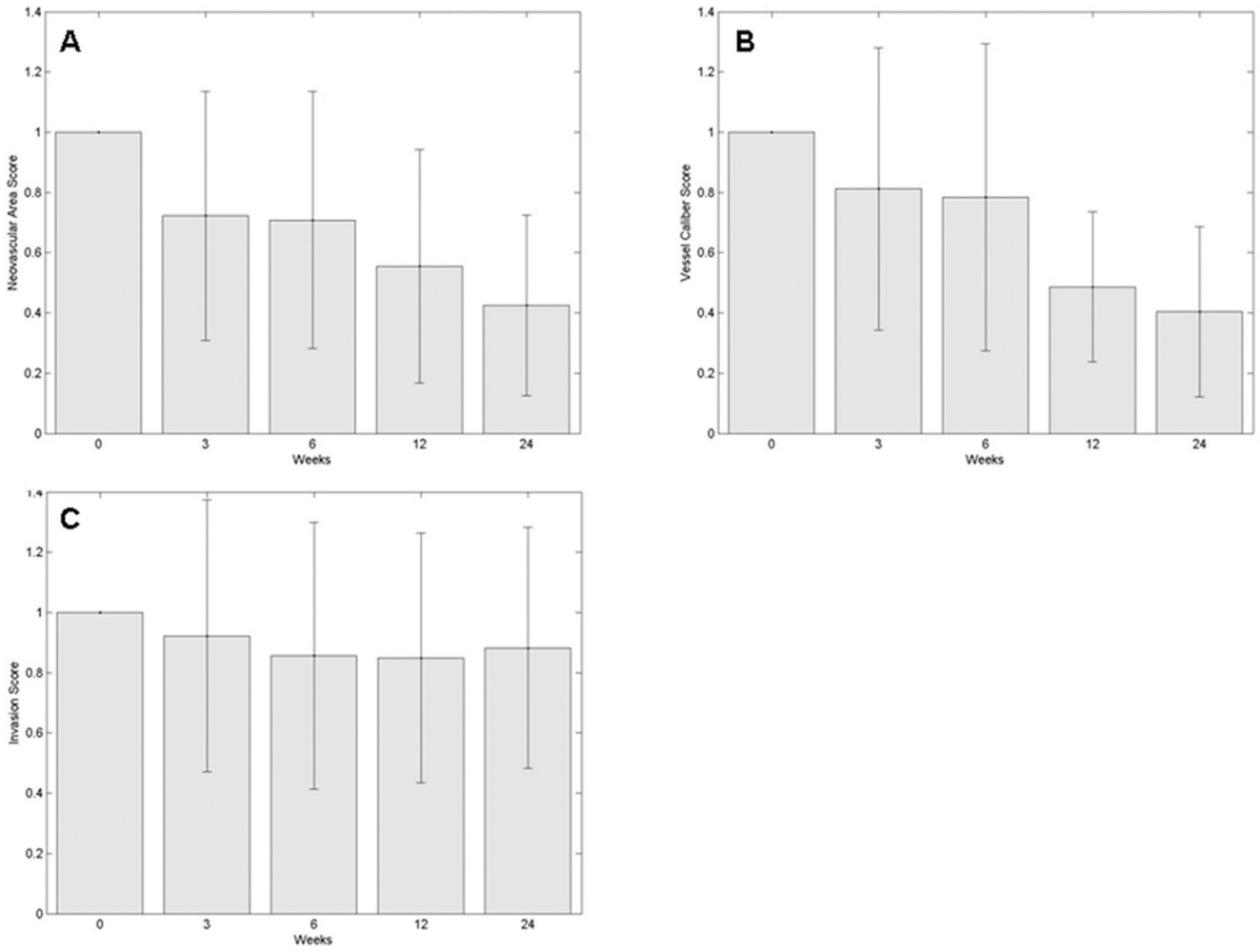

Figure 2.

Summary of changes in: **A**, Neovascular Area (NA), **B**, Vessel Caliber (VC), and **C**, Invasion Area (IA) for all patients at different time points in response to bevacizumab therapy (mean value ± standard deviation). By the last visit, the mean reduction was 47.1% ± 36.7% for NA, 54.1% ± 28.1% for VC, and 12.2% ± 42.0% for IA. The decreases in NA and VC were statistically significant. However, the levels of decrease varied significantly in different patients which were evidenced by high standard deviations in all 3 neovascularization metrics.

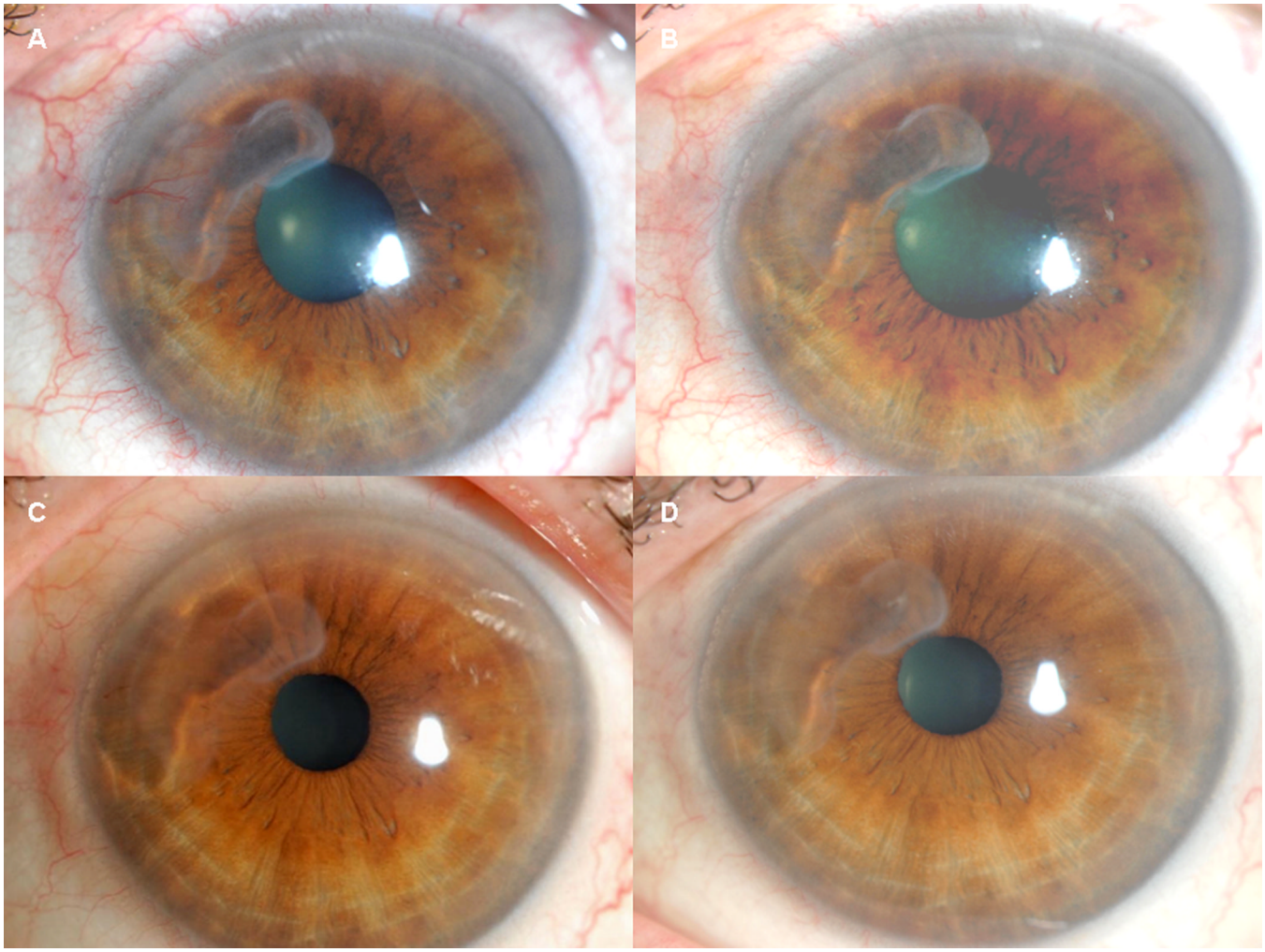

Figure 3.
The effect of topical bevacizumab in patient 6, a 65-year-old woman with history of herpes zoster ophthalmicus in the left eye complicated by corneal thinning, scarring, and neovascularization. **A**, Baseline picture shows a main vessel branch emerging from the 9-o'clock position at the limbus and passing into the thin, depressed scar in the corneal mid-periphery where it branched several times into smaller-caliber vessels. **B, C**, and **D**, One, 6, and 24 weeks after topical bevacizumab treatment. Note the significant therapeutic response which was evidenced as early as 1 week after initiation of anti-VEGF treatment.

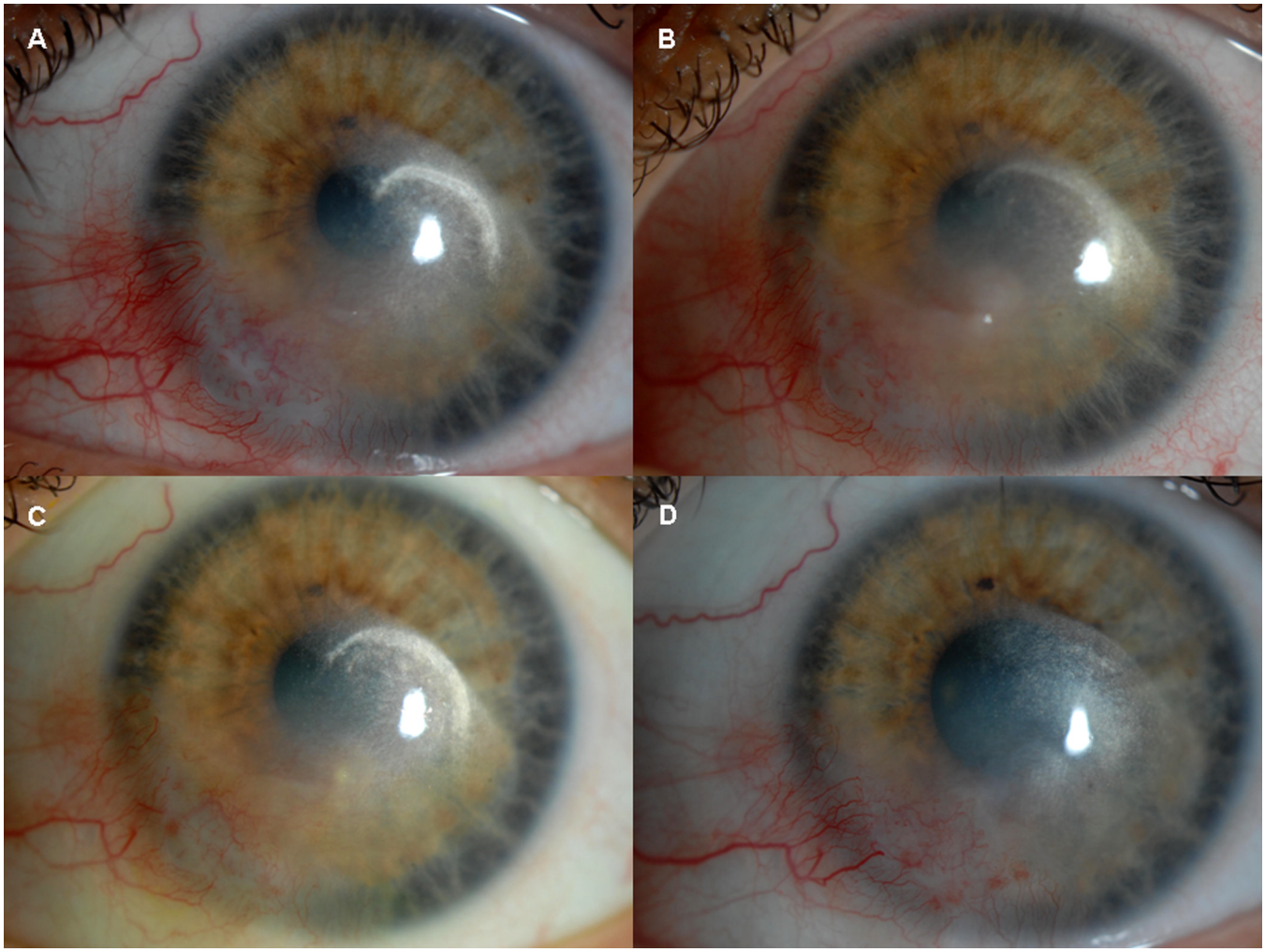

Figure 4.
The effect of topical bevacizumab in patient 7, a 39-year-old woman with history of LASIK surgery and partial limbal stem cell deficiency in the left eye complicated by corneal neovascularization. **A**, Baseline picture shows superficial and deep corneal neovascularization with central lipid keratopathy. **B, C**, and **D**, Three, 12 and 24 weeks after topical bevacizumab treatment. Note the significant narrowing of blood vessels in response to anti-VEGF treatment.

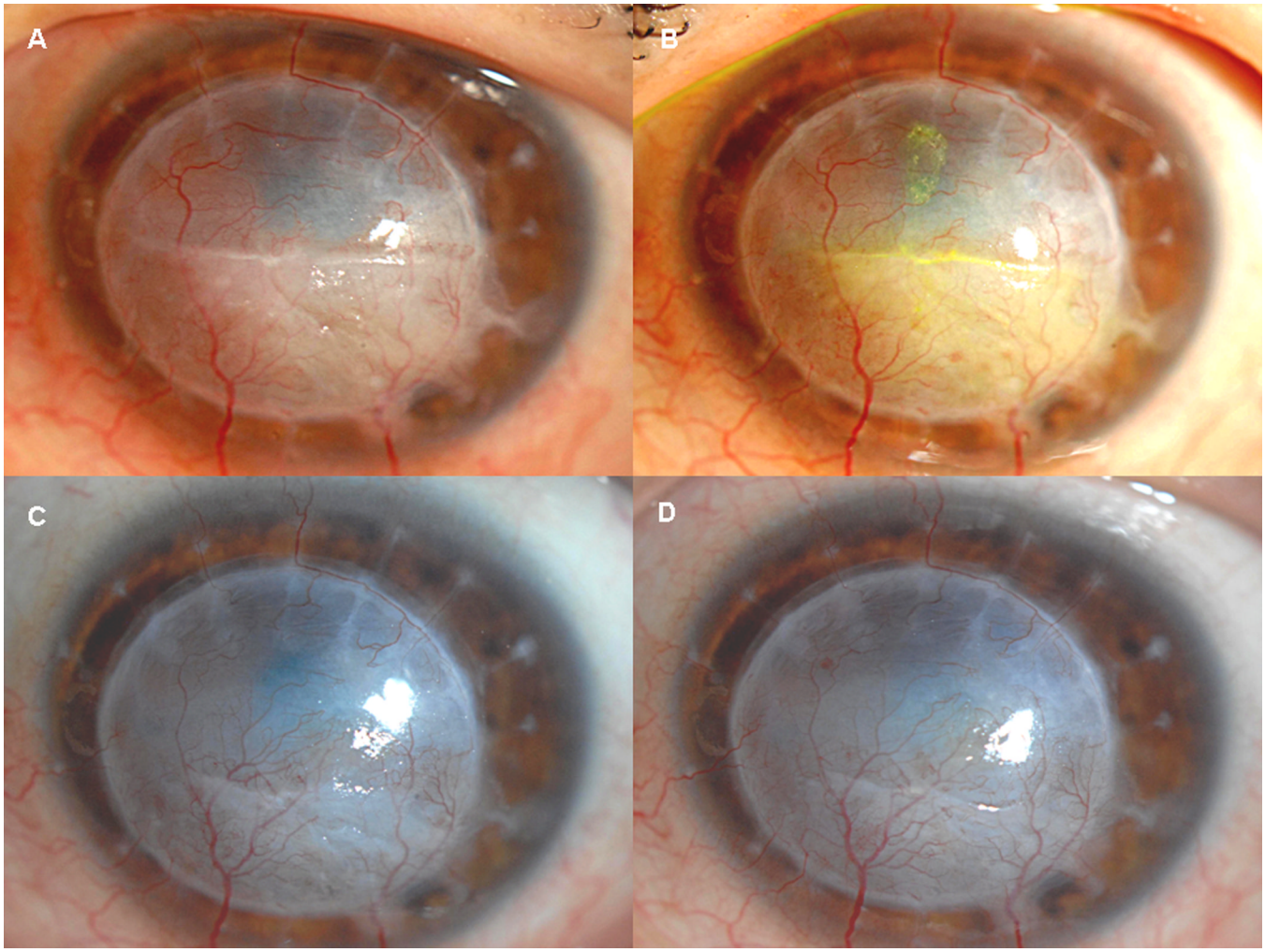

Figure 5.
The effect of topical bevacizumab in patient 8, a 42-year-old man with failed penetrating keratoplasty in the left eye complicated by corneal neovascularization. **A**, Baseline picture shows corneal opacity with severe superficial and deep corneal neovascularization. **B, C**, and **D**, Three, 12, and 24 weeks after topical bevacizumab treatment. Note the very modest therapeutic response to the anti-VEGF treatment.

Table 1

Exclusion Criteria

Age ≥ 75*
Uncontrolled hypertension* defined as systolic blood pressure of ≥150 mmHg or diastolic blood pressure of ≥90 mmHg
History of a thromboembolic events, * including myocardial infarction or cerebral vascular accident
Diabetes Mellitus*
Renal, liver, and coagulation abnormalities including current anticoagulation medications other than aspirin
Current or recent (≤1 month) systemic corticosteroid therapy or periocular corticosteroid injections to the study eye
Recent (≤1 month) change in dose and frequency of topical steroids and/or non-steroidal anti-inflammatory agents
Ocular or periocular malignancy
Pregnancy (positive pregnancy test) or lactation, and premenopausal women not using adequate contraception
Recent (≤3 months) or planned surgery
Received any other investigational therapy or treatment with anti-VEGF agents (intraocular or systemic) within 60 days prior to study entry
Any condition (including language barrier) that precludes patient's ability to comply with study requirements including completion of study

*To minimize the risk of potential systemic adverse events (hypertension and thrombosis) related to bevacizumab

Table 2

Patient Demographic Data

Patient	Eye	Gender	Age	Background Ocular Surface Disease for Corneal Neovascularization	Freq. Topical Bevacizumab
1	OS	F	50	HSV keratitis	BID*
2	OD	F	73	Secondary Sjogren's syndrome (rheumatoid arthritis), status post PK/AMT for corneal melting	BID
3	OD	F	51	HSV keratitis	BID
4	OS	M	41	LSCD, status post superficial keratectomy/ autologous limbal stem cell transplant with AMT	QID*
5	OD	F	48	Status post pterygium excision with conjunctival autograft	QID
6	OS	F	65	HZO keratitis	QID
7	OS	F	39	Status post LASIK surgery, partial LSCD	BID
8	OS	M	42	Failed PK	BID
9	OS	M	24	Rosacea blepharitis/MGD	QID
10	OS	M	40	Status post LASIK surgery, HSV keratitis	QID

OD= Right eye. OS= Left eye. F= Female. M=Male. HSV= Herpes simplex virus. PK= Penetrating keratoplasty. AMT= Amniotic membrane transplantation. LSCD= Limbal stem cell deficiency. HZO= Herpes zoster opthalmicus. LASIK= laser-assisted in situ keratomileusis. MGD= Meibomian gland dysfunction. BID= Two times a day. QID= Four times a day.

*Dose escalation from BID to QID after 5 patients completed the treatment course with no adverse events.

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